Amendments to the Specification

Please replace the paragraph beginning at page 2, line 26 with the following amended paragraph:

The present invention provides a crystal of ER-β complexed with genistein, as well as the three dimensional structure of ER-β as derived by x-ray diffraction data of the ER-β/genistein crystal. Specifically, the three dimensional structure of ER-β is defined by the structural coordinates shown in ~~Figure 2~~ FIGS. 2A-2XX, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å. The structural coordinates of ER-β are useful for a number of applications, including, but not limited to, the visualization, identification and characterization of various active sites of ER-β, and the ER-β/genistein complex, including the genistein binding site. The active site structures may then be used to design various agents which interact with ER-β, as well as ER-β complexed with genistein or related molecules.

Please replace the paragraph beginning at page 3, line 8 with the following amended paragraph:

The present invention is also directed to an active site of a genistein binding protein or peptide, and preferably the genistein binding site of the ER-β, comprising the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, ARG394, PHE404, ILE421, ILE424, GLY520,HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. Alternatively, the active site may include, in addition to the structural coordinates define above, the relative structural coordinates of amino acid residues VAL328, MET342, SER345, THR347, LYS348, LEU349, ALA350, ASP351, LEU354, MET357, TRP383, GLU385, VAL386, MET389, GLY390, LEU391, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525,

ASN526, MET527, LYS528, VAL533, VAL535, TYR536 and LEU538 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. The genistein active site may correspond to the configuration of ER-β in its state of association with an agent, preferably, genistein, or in its unbound state.

Please replace the paragraph beginning at page 3, line 26 with the following amended paragraph:

In another embodiment, the active site of a genistein binding protein or peptide, and preferably the genistein binding site of the ER-β, comprises the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, LEU391, ARG394, PHE404, ILE421, ILE424, GLY520,HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. Alternatively, the active site may include, in addition to the structural coordinates define above, the relative structural coordinates of amino acid residues MET342, SER345, THR347, LYS348, ALA350, ASP351, MET357, TRP383, GLU385, VAL386, LEU387, MET389, GLY390, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, TYR536 and LEU538 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. Here again, the genistein active site may correspond to the configuration of ER-β in its state of association with an agent, preferably, genistein, or in its unbound state.

Please replace the paragraph beginning at page 4, line 14 with the following amended paragraph:

In addition, the present invention provides a method for identifying an agent that interacts with ER-β, comprising the steps of: (a) generating a three dimensional model of ER-β using the

relative structural coordinates according to ~~Figure 2~~ FIGS. 2A-2XX, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å; and (b) employing said three-dimensional model to design or select an agent that interacts with ER-β.

Please replace the paragraph beginning at page 4, line 21 with the following amended paragraph:

Still further the present invention provides a method for identifying an activator or inhibitor of a molecule or molecular complex comprising a genistein binding site, comprising the steps of: (a) generating a three dimensional model of said molecule or molecular complex comprising a genistein binding site using (i) the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, ARG394, PHE404, ILE421, ILE424, GLY520,HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, or (ii) the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, LEU391, ARG394, PHE404, ILE421, ILE424, GLY520,HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å; and (b) selecting or designing a candidate activator or inhibitor by performing computer fitting analysis of the candidate activator or inhibitor with the three dimensional model generated in step (a). In another embodiment, the relative structural coordinates according to (i) further comprises the relative structural coordinates of amino acid residues VAL328, MET342, SER345, THR347, LYS348, LEU349, ALA350, ASP351, LEU354, MET357, TRP383, GLU385, VAL386, MET389, GLY390, LEU391, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, VAL535, TYR536 and LEU538 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. In yet another embodiment, the relative structural coordinates

according to (ii) further comprises the relative structural coordinates of amino acid residues MET342, SER345, THR347, LYS348, ALA350, ASP351, MET357, TRP383, GLU385, VAL386, LEU387, MET389, GLY390, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, TYR536 and LEU538 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

Please replace the paragraph beginning at page 6, line 1 with the following amended paragraph:

~~Figure 1~~ FIG. 1 provides a sequence alignment of ER-α with ER-β covering the ordered extent of ER-β. The numbering scheme used was chosen to be consistent with ER-α, such that the first ordered ER-β residue, 311 is residue 263 in the full length protein. Residues in helix 12 are underlined. The (*) symbols indicate the altered binding site residues.

Please replace the paragraph beginning at page 6, line 7 with the following amended paragraph:

~~Figure 2~~ FIGS. 2A-2XX provides the atomic structural coordinates for ER-β and genestein as derived by X-ray diffraction of an ER-β and genestein crystal complex. "Atom type" refers to the atom whose coordinates are being measured. "Residue" refers to the type of residue of which each measured atom is a part - i.e., amino acid, cofactor, ligand or solvent. The "x, y and z" coordinates indicate the Cartesian coordinates of each measured atom's location in the unit cell (Å). "Occ" indicates the occupancy factor. "B" indicates the "B-value", which is a measure of how mobile the atom is in the atomic structure ($Å^2$). Under "Residue type", "GEN C" refers to one molecule of genistein, "GEN D" refers to a second molecule of genistein, and "W" refers to water molecules.

Please replace the paragraph beginning at page 6, line 20 with the following amended paragraph:

Unless otherwise noted, Estrogen Receptor-β (ER-β) comprises the amino acid sequence depicted in ~~Figure 1~~ FIG. 1, including conservative substitutions.

Please replace the paragraph beginning at page 7, line 3 with the following amended paragraph:

"Structural coordinates" are the Cartesian coordinates corresponding to an atom's spatial relationship to other atoms in a molecule or molecular complex. Structural coordinates may be obtained using x-ray crystallography techniques or NMR techniques, or may be derived using molecular replacement analysis or homology modeling. Various software programs allow for the graphical representation of a set of structural coordinates to obtain a three dimensional representation of a molecule or molecular complex. The structural coordinates of the present invention may be modified from the original sets provided in ~~Figure 2~~ FIGS. 2A-2XX by mathematical manipulation, such as by inversion or integer additions or subtractions. As such, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of ~~Figure 2~~ FIGS. 2A-2XX.

Please replace the paragraph beginning at page 7, line 24 with the following amended paragraph:

It will be obvious to the skilled practitioner that the numbering of the amino acid residues of ER-β may be different than that set forth herein, and may contain certain conservative amino acid substitutions that yield the same three dimensional structures as those defined by ~~Figure 2~~ FIGS. 2A-2XX herein. Corresponding amino acids and conservative substitutions in other isoforms or analogues are easily identified by visual inspection of the relevant amino acid sequences or by using commercially available homology software programs (e.g., MODELLAR, MSI, San Diego, CA).

Please replace the paragraph beginning at page 9, line 1 with the following amended paragraph:

The present invention first provides a crystallized complex comprising ER-β and genistein. In a particular embodiment, the amino acid sequence of ER-β is set forth in ~~Figure 1~~ FIG. 1, and includes conservative substitutions. The crystal complex of the present invention effectively diffracts X-rays for the determination of the structural coordinates of the complex of ER-β and genistein, and is characterized as having space group $P2_12_12_1$, and unit cell parameters of a=53.49Å, b=85.21Å, c=107.07Å. Further, the crystallized complex of the present invention consists of two molecules of ER-β each bound to a molecule of genistein.

Please replace the paragraph beginning at page 9, line 21 with the following amended paragraph:

Accordingly, the present invention also provides the three dimensional structure of ER-β as derived by x-ray diffraction data of the ER-β/genistein crystal. Specifically, the three dimensional structure of ER-β is defined by the structural coordinates shown in ~~Figure 2~~ FIGS. 2A-2XX, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å. The structural coordinates of ER-β are useful for a number of applications, including, but not limited to, the visualization, identification and characterization of various active sites of ER-β, and the ER-β/genistein complex, including the genistein binding site. The active site structures may then be used to design agents with interact with ER-β, as well as ER-β complexed with genistein or related molecules.

Please replace the paragraph beginning at page 10, line 3 with the following amended paragraph:

The present invention is also directed to an active site of a genistein binding protein or peptide, and preferably the genistein binding site of the ER-β, comprising the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387,

MET388, ARG394, PHE404, ILE421, ILE424, GLY520, HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5 Å. Alternatively, the active site may include, in addition to the structural coordinates define above, the relative structural coordinates of amino acid residues VAL328, MET342, SER345, THR347, LYS348, LEU349, ALA350, ASP351, LEU354, MET357, TRP383, GLU385, VAL386, MET389, GLY390, LEU391, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, VAL535, TYR536 and LEU538 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å. The genistein active site may correspond to the configuration of ER-β in its state of association with an agent, preferably, genistein, or in its unbound state.

Please replace the paragraph beginning at page 10, line 23 with the following amended paragraph:

In another embodiment, the active site of a genistein binding protein or peptide, and preferably the genistein binding site of the ER-β, comprises the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, LEU391, ARG394, PHE404, ILE421, ILE424, GLY520, HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å. Alternatively, the active site may include, in addition to the structural coordinates define above, the relative structural coordinates of amino acid residues MET342, SER345, THR347, LYS348, ALA350, ASP351, MET357, TRP383, GLU385, VAL386, LEU387, MET389, GLY390, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517,

LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, TYR536 and LEU538 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å. Here again, the genistein active site may correspond to the configuration of ER-β in its state of association with an agent, preferably, genistein, or in its unbound state.

Please replace the paragraph beginning at page 11, line 13 with the following amended paragraph:

Another aspect of the present invention is directed to a method for identifying an agent that interacts with ER-β, comprising the steps of: (a) generating a three dimensional model of ER-β using the relative structural coordinates according to ~~Figure 2~~ FIGS. 2A-2XX, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å; and (b) employing said three-dimensional model to design or select an agent that interacts with ER-β. The agent may be identified using computer fitting analyses utilizing various computer software programs that evaluate the "fit" between the putative active site and the identified agent, by (a) generating a three dimensional model of the putative active site of a molecule or molecular complex using homology modeling or the atomic structural coordinates of the active site, and (b) determining the degree of association between the putative active site and the identified agent. Three dimensional models of the putative active site may be generated using any one of a number of methods known in the art, and include, but are not limited to, homology modeling as well as computer analysis of raw data generated using crystallographic or spectroscopy data. Computer programs used to generate such three dimensional models and/or perform the necessary fitting analyses include, but are not limited to: GRID (Oxford University, Oxford, UK), MCSS (Molecular Simulations, San Diego, CA), AUTODOCK (Scripps Research Institute, La Jolla, CA), DOCK (University of California, San Francisco, CA), Flo99 (Thistlesoft, Morris Township, NJ), Ludi (Molecular Simulations, San Diego, CA), QUANTA (Molecular

Simulations, San Diego, CA), Insight (Molecular Simulations, San Diego, CA), SYBYL (TRIPOS, Inc., St. Louis. MO) and LEAPFROG (TRIPOS, Inc., St. Louis, MO). The structural coordinates also may be used to visualize the three-dimensional structure of ER-β and the ER-β/genistein complex using MOLSCRIPT (28) and RASTER3D (29), for example.

Please replace the paragraph beginning at page 12, line 21 with the following amended paragraph:

The present invention also provides a method for identifying an activator or inhibitor of a molecule or molecular complex comprising a genistein binding site, and preferably ER-β, comprising the steps of: (a) generating a three dimensional model of said molecule or molecular complex comprising a genistein binding site using (i) the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, ARG394, PHE404, ILE421, ILE424, GLY520, HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5 Å, or (ii) the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, LEU391, ARG394, PHE404, ILE421, ILE424, GLY520,HIS523 and LEU524 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å; and (b) selecting or designing a candidate activator or inhibitor by performing computer fitting analysis of the candidate activator or inhibitor with the three dimensional model generated in step (a). In another embodiment, the structural coordinates according to (i) further comprises the relative structural coordinates of amino acid residues VAL328, MET342, SER345, THR347, LYS348, LEU349, ALA350, ASP351, LEU354, MET357, TRP383, GLU385, VAL386, MET389, GLY390, LEU391, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, VAL535, TYR536 and LEU538

according to ~~Figure 2~~ FIGS. 2A-2XX for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å. In yet another embodiment, the relative structural coordinates according to (ii) further comprises the relative structural coordinates of amino acid residues MET342, SER345, THR347, LYS348, ALA350, ASP351, MET357, TRP383, GLU385, VAL386, LEU387, MET389, GLY390, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, TYR536 and LEU538 according to ~~Figure 2~~ FIGS. 2A-2XX for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å. Once the candidate activator or inhibitor is obtained or synthesized, the candidate activator or inhibitor may be contacted with the molecule or molecular complex, and the effect the candidate activator or inhibitor has on said molecule or molecular complex may be determined. Preferably, the candidate activator or inhibitor is contacted with the molecule or molecule complex in the presence of genistein (or a molecule or a molecular complex comprising genistein) in order to determine the effect the candidate activator or inhibitor has on binding of the molecule or molecular complex to genistein.